Genetics and update of CKD

Hussein Sheashaa, MD, FACP

Professor of Nephrology, Urology and Nephrology Center and Director of Medical E-Learning Unit, Mansoura University and Executive Director of ESNT- Virtual Academy: http://lms.mans.edu.eg/esnt/

ESNT, February 23rd , 2016

Nephrogenetics

Urology and Nephrology Center

Mallett *et al. Human Genomics* (2015) 9:13
DOI 10.1186/s40246-015-0035-1

Human Genomics

OPINION ARTICLE Open Access

Genomics in the renal clinic - translating nephrogenetics for clinical practice

Andrew Mallett[1,2,3*], Christopher Corney[1,2], Hugh McCarthy[4,5], Stephen I. Alexander[4,5,6] and Helen Healy[1,2]

Corners

1. Early onset CKD
2. Alternative splicing
3. DKD and hypertension
4. ADPCKD
5. African American and kidney disease
6. Clinical implications and guidelines
7. Closure

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Early Onset CKD

Early Onset CKD: Exploring the Genes

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REVIEWS

Exploring the genetic basis of early-onset chronic kidney disease

Asaf Vivante[1,2] and Friedhelm Hildebrandt[1]

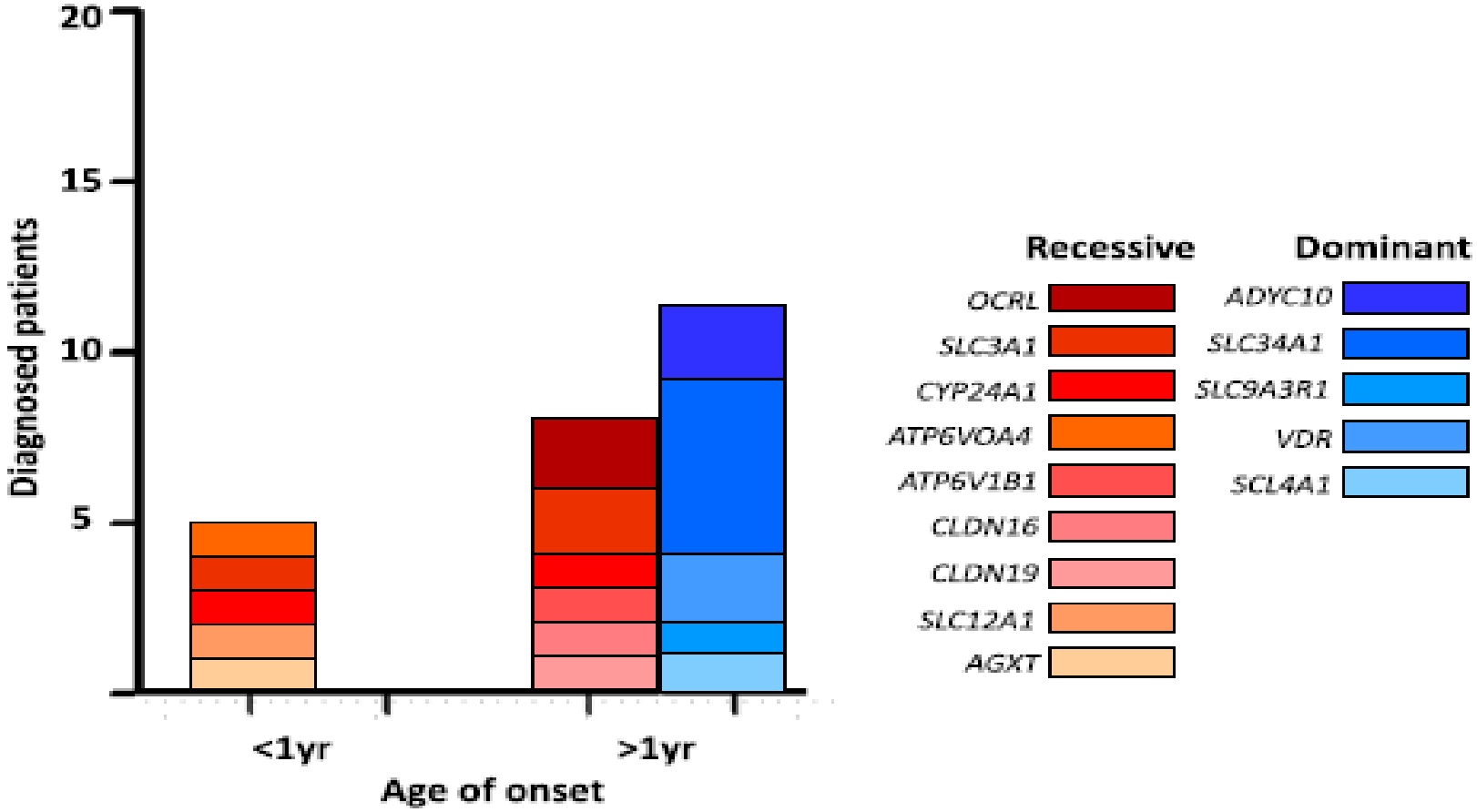
Nature Reviews | Nephrology Published Online 11 Jan 2016

Early Onset CKD: Exploring the Genes

Diagnostic group	Indication to run a gene panel	Proportion of cases of early-onset CKD	Number of known causative genes	Percentage of cases caused by known genes (multiplied by fraction of all CKD)
aHUS	Microangiopathic haemolytic anaemia, thrombocytopaenia, and AKI	2.0%	9	~60% (1.2%)
Nephrolithiasis or nephrocalcinosis	Known stone disease or nephrocalcinosis	1.6% (cystinosis 1.5%; oxalosis 0.1%)	30	21% (0.4%)
Other	Other indications of genetic disease	23.5% (renal infarct 2.2%; pyelonephritis or interstitial nephritis 1.4%; Wilms tumour 0.5%; other systemic immunologic diseases 0.4%; granulomatosis with polyangiitis 0.4%; sickle cell nephropathy 0.2%; diabetic glomerulopathy 0.2%; other nonimmunologic causes 18.2%)	Not known	Not known
Total	—	100%	~219	(~20%)

Nature Reviews | Nephrology Published Online 11 Jan 2016

Urinary Stones:
Monogenic Causes



CJASN ePress. Published on January 19, 2016

Increased Echogenicity: The Causative Mutations

Urology and Nephrology Center

Whole exome sequencing identifies causative mutations in the majority of consanguineous or familial cases with childhood-onset increased renal echogenicity

Daniela A. Braun[1,19], Markus Schueler[1,19], Jan Halbritter[1,2], Heon Yung Gee[1], Jonathan D. Porath[1], Jennifer A. Lawson[1], Rannar Airik[1], Shirlee Shril[1], Susan J. Allen[3], Deborah Stein[1], Adila Al Kindy[4], Bodo B. Beck[5], Nurcan Cengiz[6], Khemchand N. Moorani[7], Fatih Ozaltin[8,9,10], Seema Hashmi[11], John A. Sayer[12], Detlef Bockenhauer[13], Neveen A. Soliman[14,15], Edgar A. Otto[3], Richard P. Lifton[16,17,18] and Friedhelm Hildebrandt[1,18]

[1]Division of Nephrology, Department of Medicine, Boston Children's Hospital, Harvard Medical School, Boston, Massachusetts, USA; [2]Division of Nephrology, Department of Internal Medicine, University Clinic Leipzig, Leipzig, Germany; [3]Department of Pediatrics, University of Michigan, Ann Arbor, Michigan, USA; [4]Department of Genetics, Sultan Qaboos University Hospital, Seeb, Sultanate of Oman; [5]Institute for Human Genetics, University of Cologne, Cologne, Germany; [6]School of Medicine, Adana Medical Training and Research Center, Department of Pediatric Nephrology, Baskent University, Adana, Turkey; [7]Department of Pediatric Nephrology, National Institute of Child Health, Karachi, Pakistan; [8]Faculty of Medicine, Department of Pediatric Nephrology, Hacettepe University, Ankara, Turkey; [9]Nephrogenetics Laboratory, Faculty of Medicine, Department of Pediatric Nephrology, Hacettepe University, Ankara, Turkey; [10]Center for Biobanking and Genomics, Hacettepe University, Ankara, Turkey; [11]Department of Pediatric Nephrology, Sindh Institute of Urology and Transplantation, SIUT, Karachi, Pakistan; [12]Institute of Genetic Medicine, International Centre for Life, Newcastle University, Central Parkway, Newcastle, UK; [13]University College London, Institute of Child Health and Pediatric Nephrology, Great Ormond Street Hospital for Children NHS Foundation Trust, London, UK; [14]Department of Pediatrics, Kasr Al Ainy School of Medicine, Cairo University, Cairo, Egypt; [15]Egyptian Group for Orphan Renal Diseases (EGORD), Cairo, Egypt; [16]Department of Genetics, Yale University School of Medicine, New Haven, Connecticut, USA; [17]Yale Center for Mendelian Genomics, Yale University School of Medicine, New Haven, Connecticut, USA; and [18]Howard Hughes Medical Institute, Chevy Chase, MD, USA

Kidney International (2016) 89, 468–475

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Alternative Splicing and CKD

Alternative Splicing in CKD

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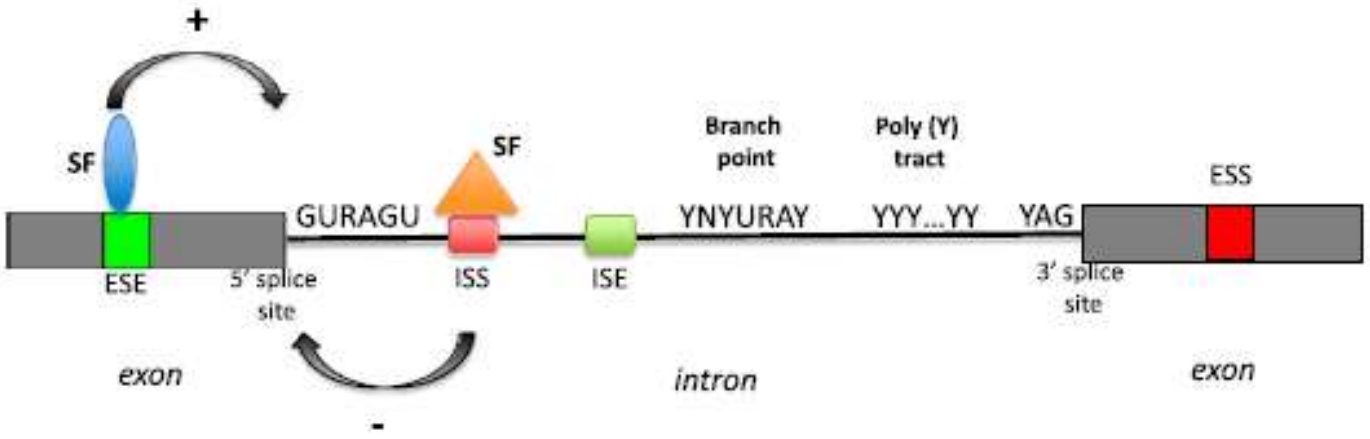
BRIEF REVIEW www.jasn.org

Alternative Splicing in CKD

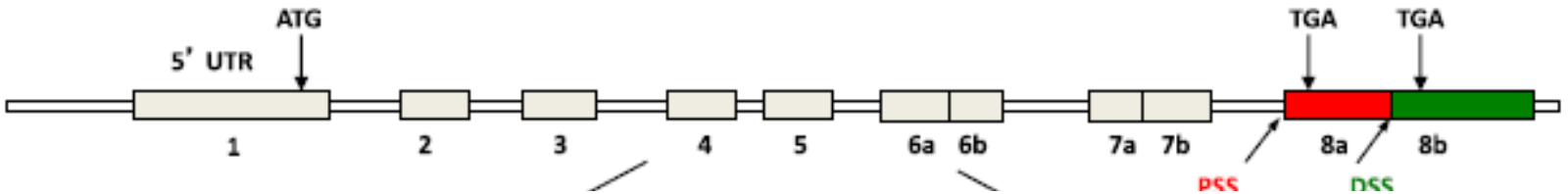
Megan Stevens*† and Sebastian Oltean*†

*School of Physiology and Pharmacology, Faculty of Biomedical Sciences, and †Academic Renal Unit, School of Clinical Sciences, Faculty of Health Sciences, University of Bristol, Bristol, United Kingdom



J Am Soc Nephrol 2016, in press

Alternative Splicing in CKD



sVEGFR-1 (Soluble Flt-1)
Soluble Klotho
Soluble Erythropoietin Receptor
Fibronectin

$VEGF_{206}b$
$VEGF_{189}b$
$VEGF_{183}b$
$VEGF_{165}b$
$VEGF_{145}b$
$VEGF_{121}b$

Proximal Splice Site - $VEGF_{xxx}$
Angiogenic

Distal Splice Site - $VEGF_{xxx}b$
Anti-Angiogenic

J Am Soc Nephrol 2016, in press

Alternative Splicing: Potential Therapy

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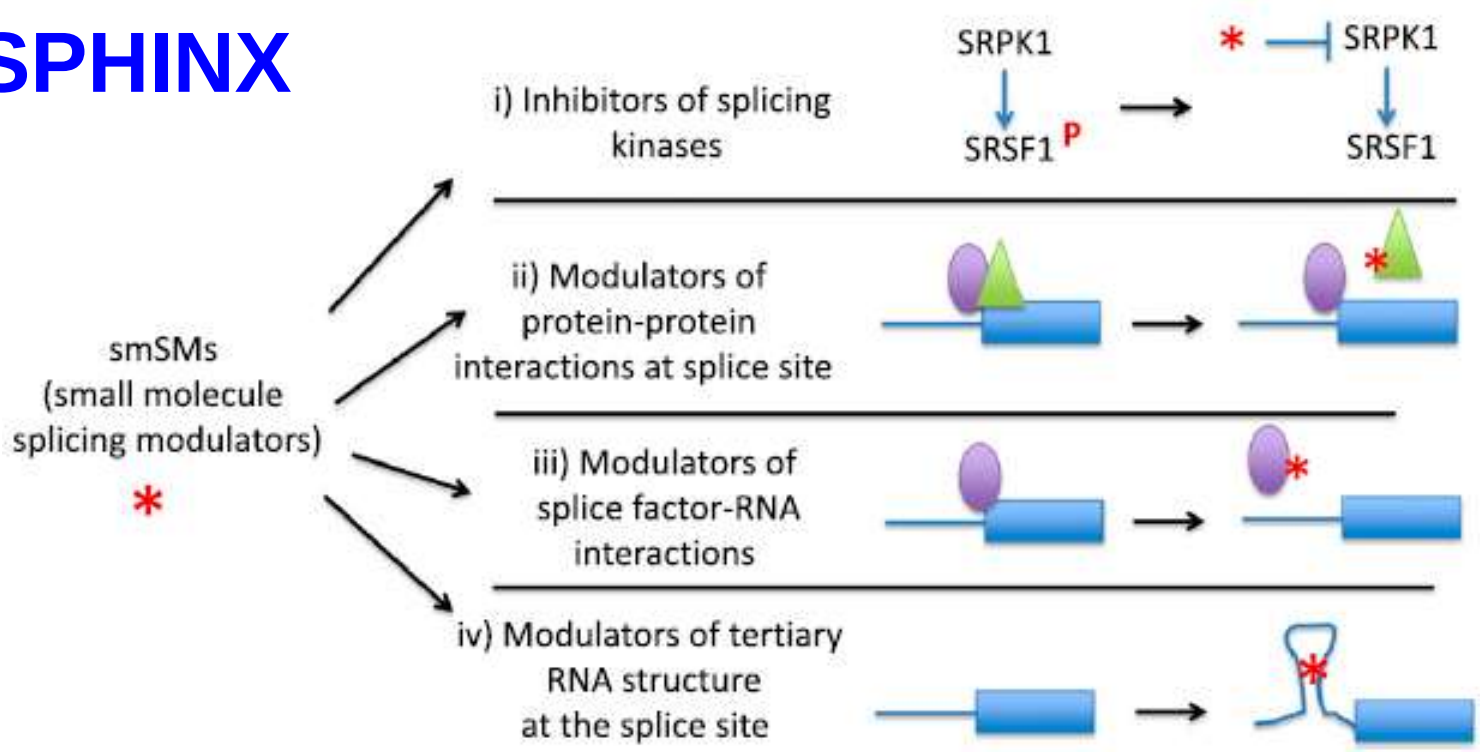
DNG

SPHINX



J Am Soc Nephrol 2016, in press

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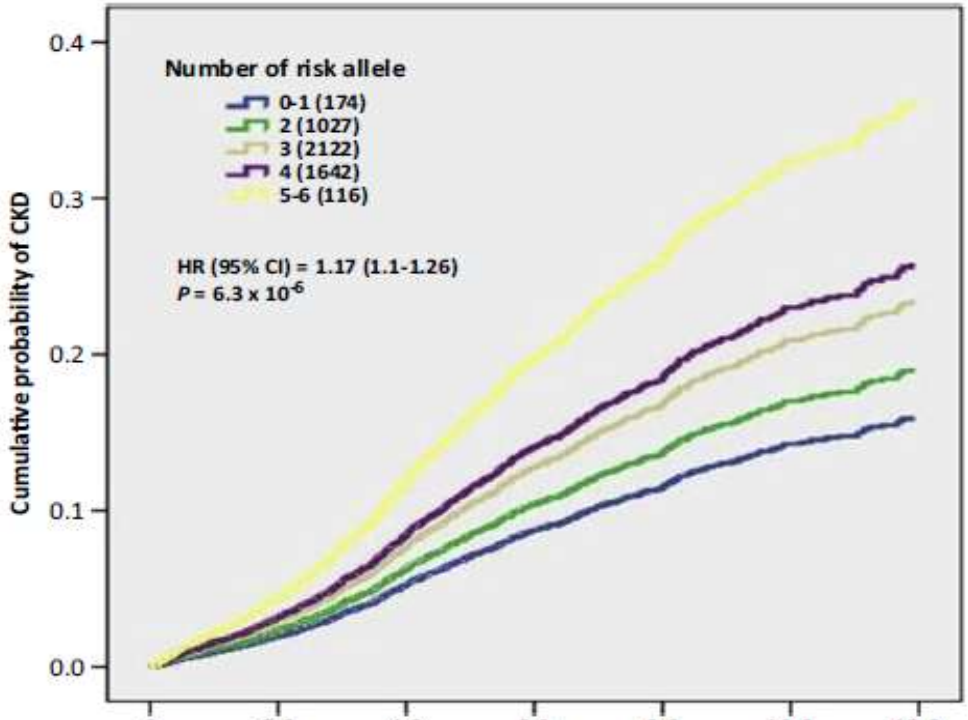
DKD and Hypertension

DKD and SNP



No. of at-risk by allele count

0-1	174	167	156	123	102	76	37
2	1027	968	922	772	569	401	170
3	2122	1996	1878	1521	1154	824	373
4	1642	1526	1438	1186	901	606	248
5-6	116	110	103	83	67	49	22

rs478333, rs7756992, rs7754840

Kidney International (2016) 89, 411–420

Epigenetic Memory in Kidney Diseases

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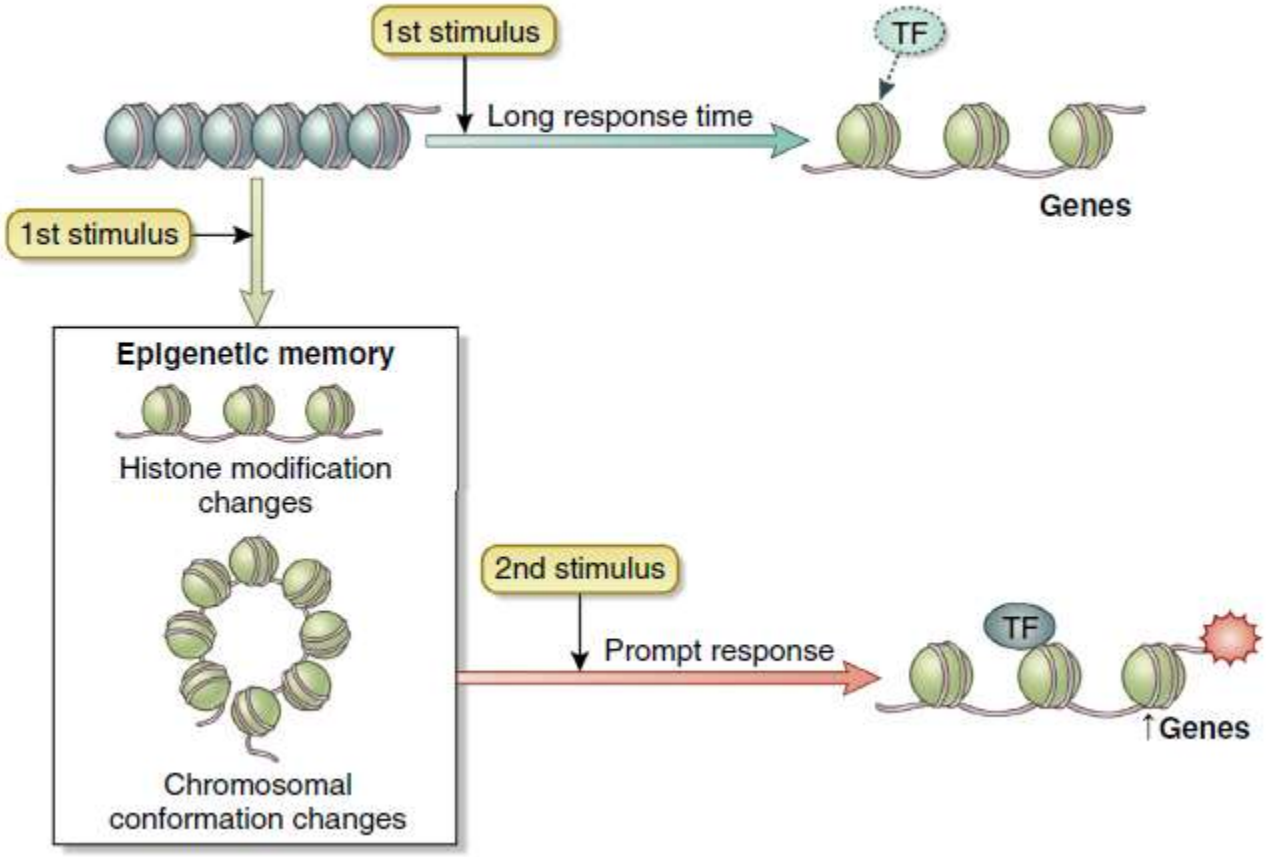
Epigenetic memory in kidney diseases

Imari Mimura[1]

Epigenetic mechanisms have been the focus of intensive research. De Marinis *et al.* demonstrated that high glucose levels exert stimulatory effects on activation histone marks, leading to the upregulation of thioredoxin-interacting protein (*TXNIP*) gene expression, which is proinflammatory. They also showed that the effect was reversed by the inhibition of histone acetyltransferase, suggesting a new therapeutic approach for improving diabetic kidney disease. Epigenetic changes are memorized as epigenetic memory that could exacerbate diabetic complications.

Kidney International (2016) **89,** 274–277; http://dx.doi.org/10.1016/j.kint.2015.12.026

Epigenetic Memory in Kidney Diseases



Kidney International (2016) 89, 274–277

Hypertension Pharmacogenomics

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Hypertension pharmacogenomics: in search of personalized treatment approaches

Rhonda M. Coope

Top pharmacogenomic signals associated with blood pressure response and/or cardiovascular outcomes

Association	Drug class	Locus (SNP)	Associated allele	Magnitude of effect
BP response and CV outcomes	Thiazide diuretic	*NEDD4L* (rs4149601)	G allele	BP lowering: G allele associated with greater BP response (−19.5 versus −15.0 mmHg SBP and −15.4 versus −14.0 mmHg DBP)[38] Adverse CV outcomes: G allele associated with reduced risk of CV outcomes in NORDIL β-blocker/diuretic arm (OR 0.52, $P<0.0001$)[38] G allele (one or two copies) associated with increased risk of CV outcomes when a thiazide diuretic was not included in treatment (OR 8.94–10.7, $P=0.051$–0.022)[39]
	β-blocker	*ADRB1* (rs1801253 [Arg389Gly])	C allele	C allele (arginine) homozygotes had greater BP response to metoprolol: −6.5 mmHg in 24 h DBP more than G (glycine) allele carriers ($P=0.0018$)[45]
		ADRB1 (rs1801252 [Ser49Gly])	A allele	A allele (serine) homozygotes had similar trend for greater DBP response to metoprolol ($P=0.08$)[45]
		ADRB1 Ser49/Arg389 haplotype	Haplotype	Ser49Arg389/Ser49Arg389 haplotype associated with greater BP response to metoprolol (−14.7 mmHg versus −0.5 mmHg in patients with the Gly49Arg389/Ser49Gly389 haplotype; $P=0.006$)[45]

CKD Progression:
RAAS genes

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The role of renin–angiotensin–aldosterone system genes in the progression of chronic kidney disease: findings from the Chronic Renal Insufficiency Cohort (CRIC) study

AGT and RENBP

Tanika N. Kelly[1], Dominic Raj[2], Mahboob Rahman[3], Matthias Kretzler[4], Radhakrishna R. Kallem[5], Ana C. Ricardo[6], Sylvia E. Rosas[7], Kaixiang Tao[8], Dawei Xie[8], Lotuce Lee Hamm[9] and Jiang He[1,9] on behalf of the CRIC Study Investigators*

[1]School of Public Health and Tropical Medicine, Tulane University, New Orleans, LA 70112, USA, [2]Medical Faculty Associates, George Washington University, Washington, DC 20037, USA, [3]University Hospitals Case Medical Center, Case Western Reserve University, Louis Stokes Cleveland VA Medical Center, Cleveland, OH 44106, USA, [4]University of Michigan, Ann Arbor, MI 48109, USA, [5]University of Pennsylvania, Translational Research Center, Philadelphia, PA 19104, USA, [6]University of Illinois at Chicago, Chicago, IL 60612, USA, [7]Joslin Diabetes Center, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA 02215, USA, [8]The Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA 19104, USA and [9]Tulane University School of Medicine, New Orleans, LA 70112, USA

Nephrol Dial Transplant (2015) 30: 1711–1718

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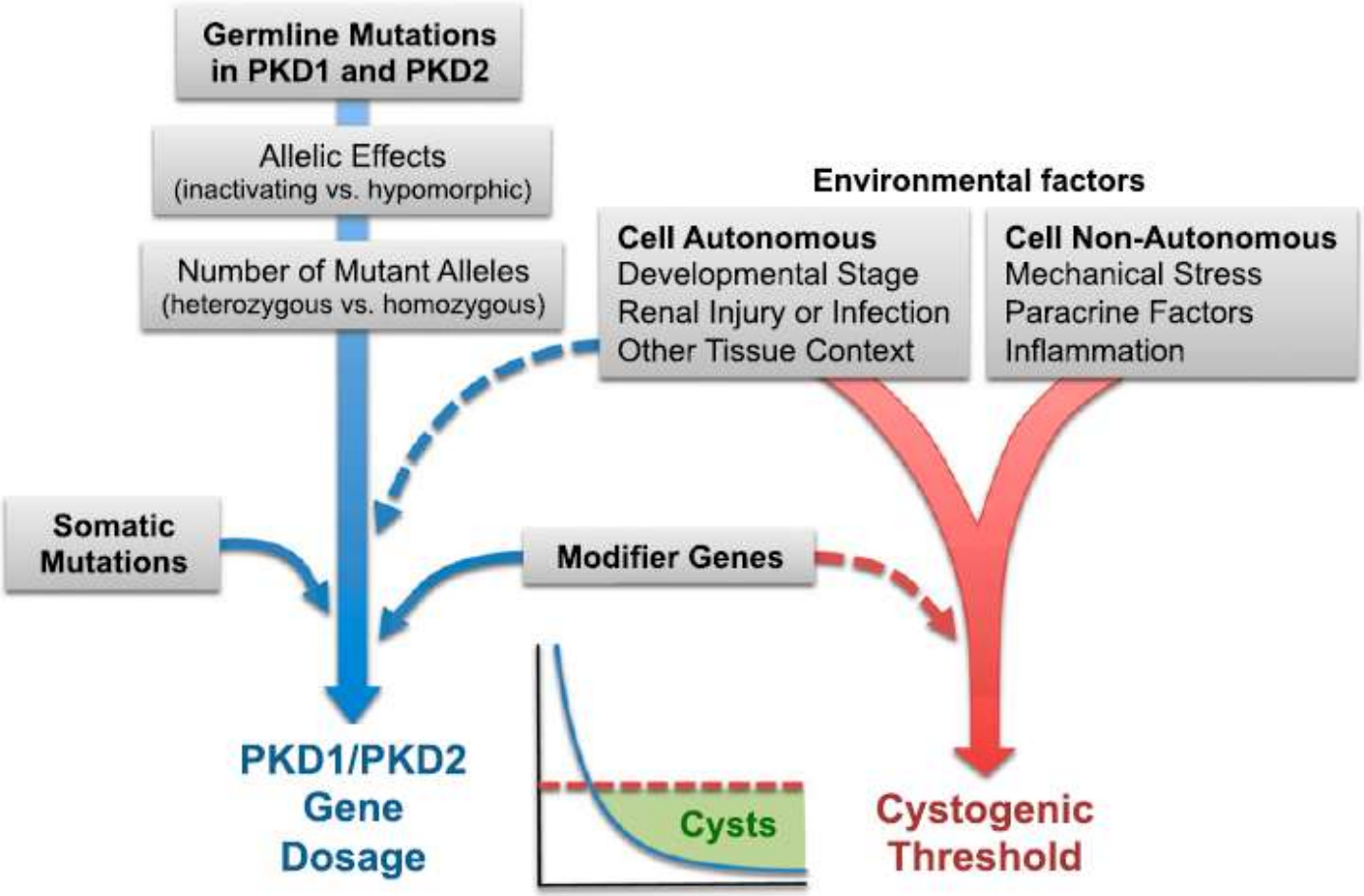
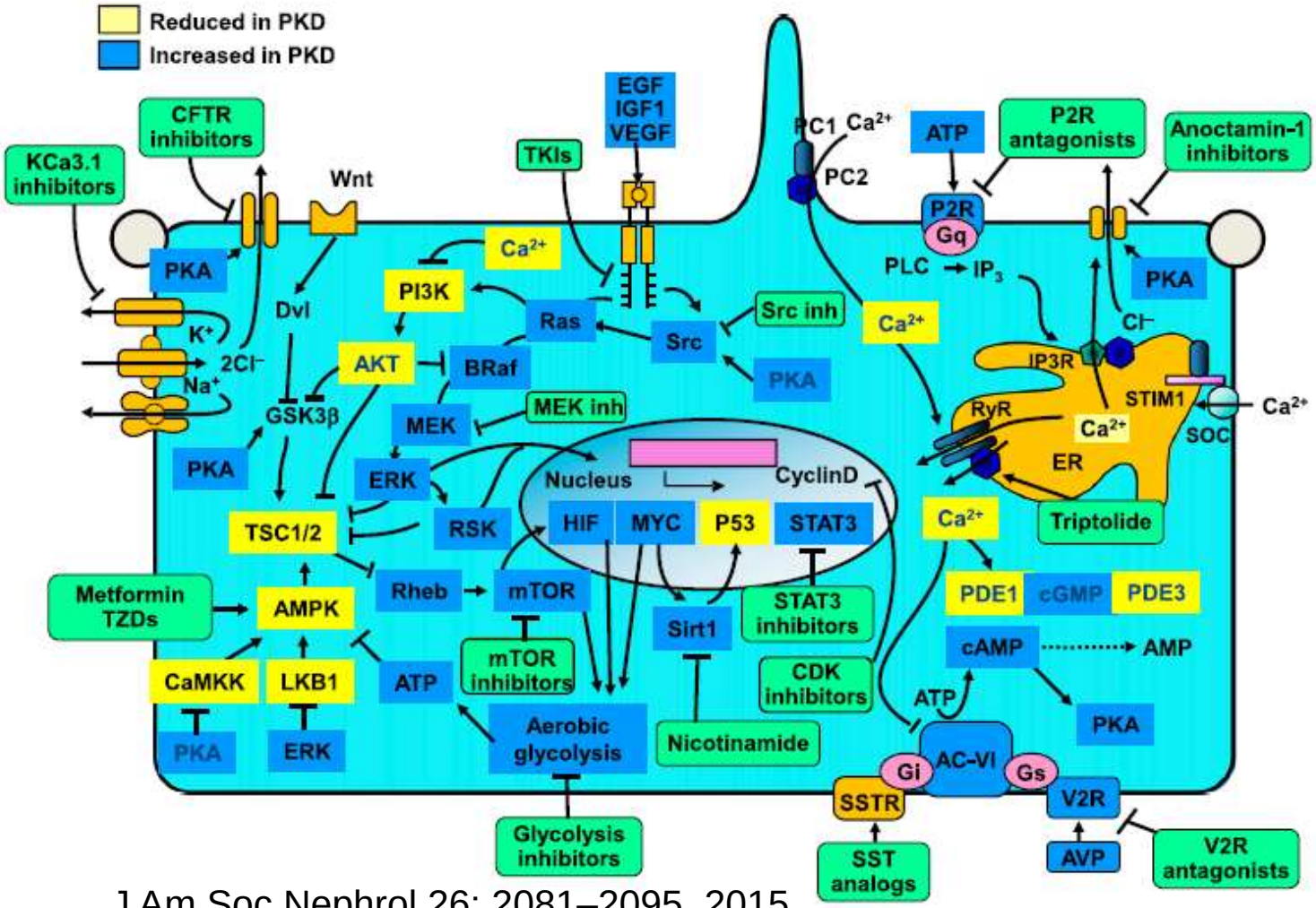
ADPCKD

ADPCKD:
Cystogenesis



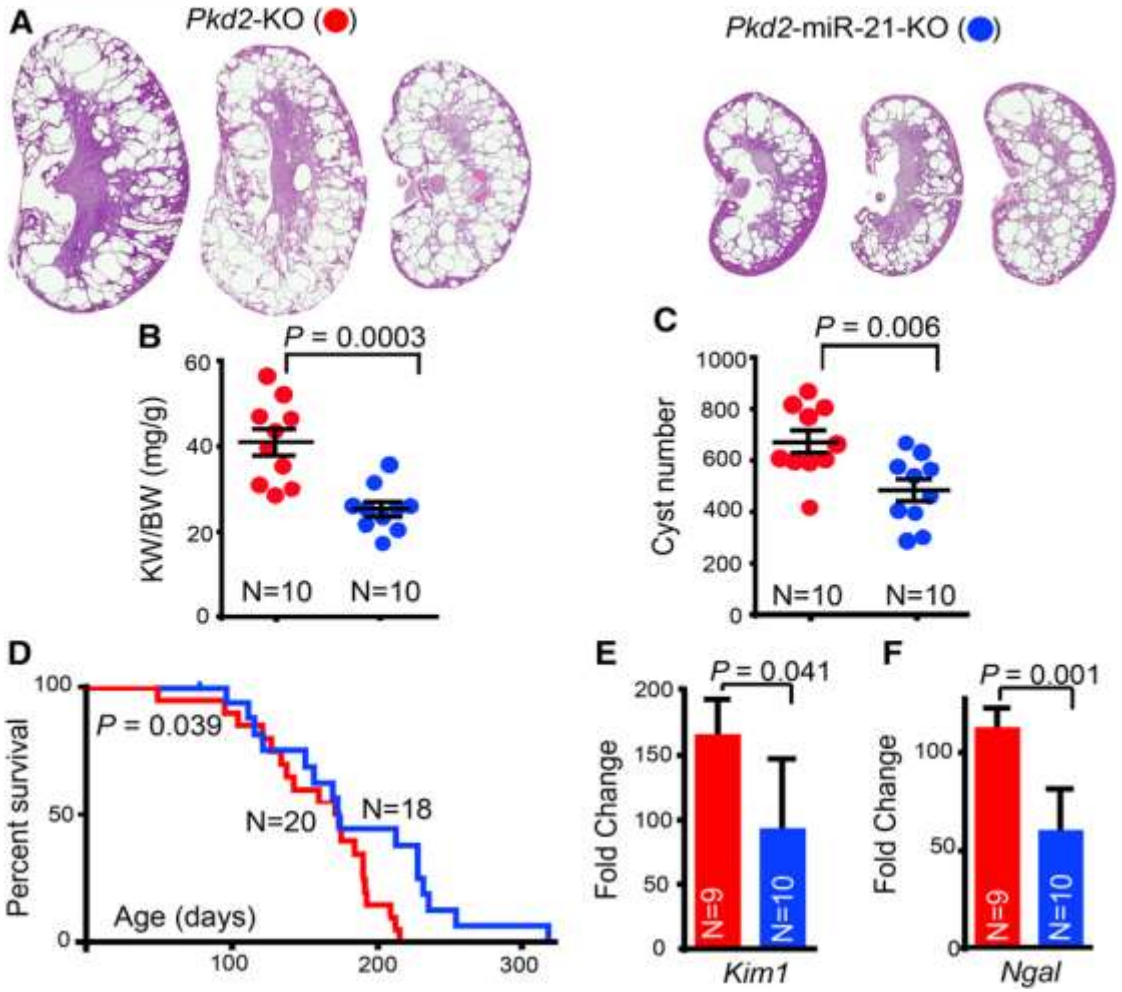
J Am Soc Nephrol 26: 2081–2095, 2015

ADPCKD:
Cystogenesis



J Am Soc Nephrol 26: 2081–2095, 2015

PKD: MicroRNA-21



J Am Soc Nephrol 2016, in press

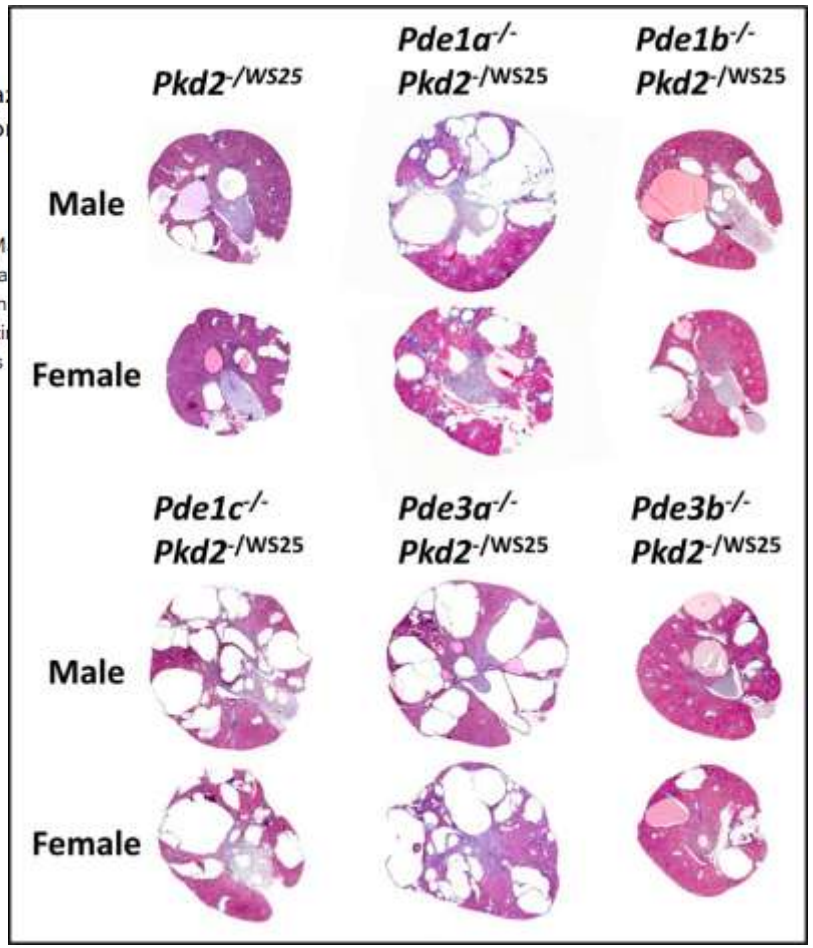
ADPCKD:
Pd1 and 3

Urology and Nephrology Center

Modulation of Polycystic Kidney Disease Severity by Phosphodiesterase 1 and 3 Subfamilies

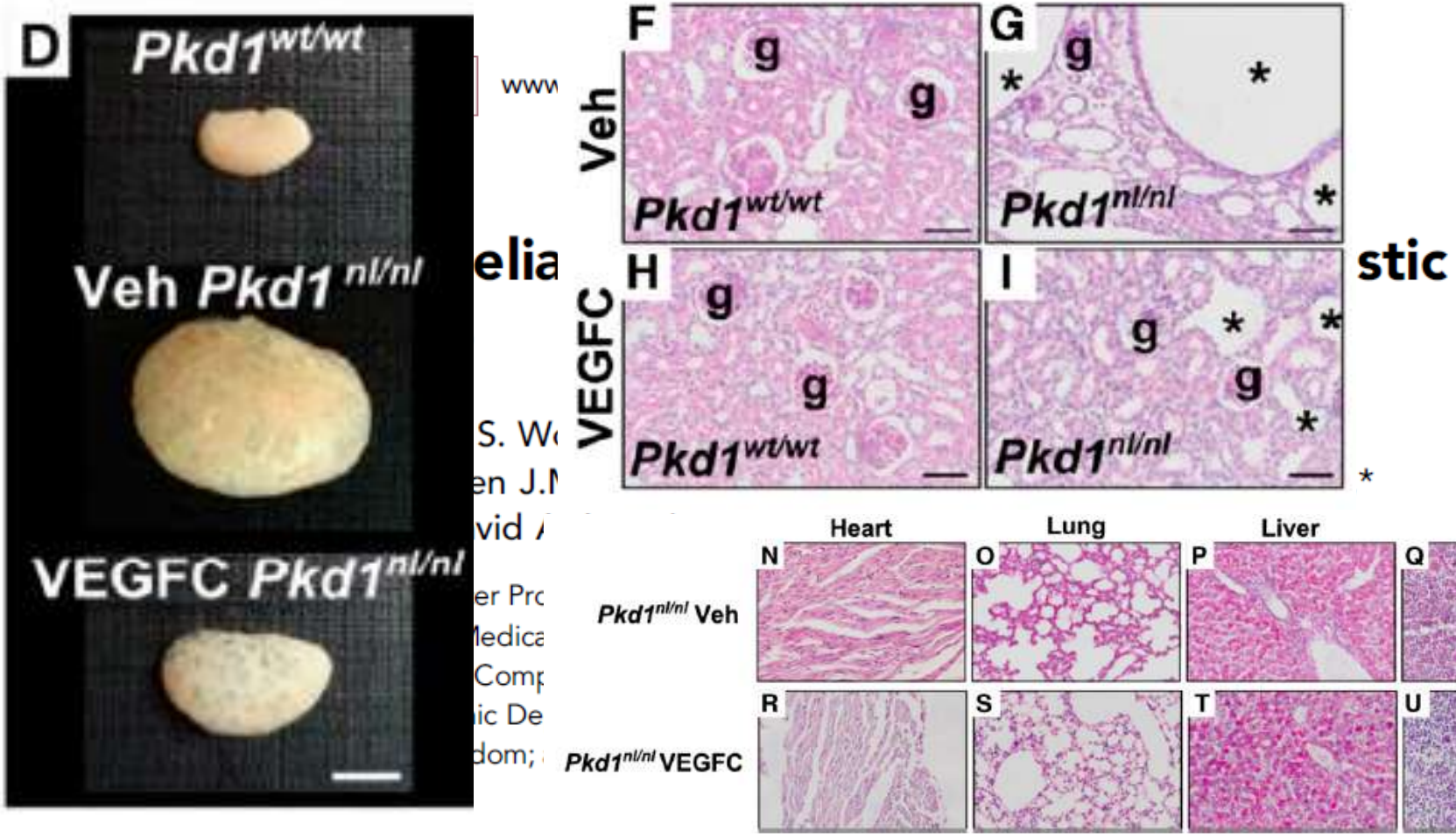
Hong Ye,* Xiaofang Wang,* Caroline R. Sussman,* Katharina Hopp,* Maria V. Ira
Jason L. Bakeberg,† Wells B. LaRiviere,* Vincent C. Manganiello,‡ Charles V. Voo
Haiqing Zhao,‖ Peter C. Harris,* Jan van Deursen,¶ Christopher J. Ward,† and
Vicente E. Torres*

*Division of Nephrology and Hypertension and ¶Department of Biochemistry and Molecular Biology, M
Rochester, Minnesota; †Division of Nephrology and Hypertension, The Kidney Institute, University of Ka
Center, Kansas City, Kansas; ‡Cardiovascular and Pulmonary Branch, National Heart, Lung and Blood In
National Institutes of Health, Bethesda, Maryland; §Department of Pediatrics, Division of Neurology, Cinci
Research Foundation and University of Cincinnati, Cincinnati, Ohio; and ‖Department of Biology, Johns
University, Baltimore, Maryland



J Am Soc Nephrol 2016, in press

ADPCKD:
VEGFC



J Am Soc Nephrol 27: 69–77, 2016

ADPCKD: Genotypes

Table 2. Age at ESRD and patient death by mutation class

Mutation Class	N	Age (yr) at ESRD[a]	Age (yr) at Patient Death[a]
PKD1 truncating	249	52.5 (51.2 to 53.9)	65.2 (62.7 to 67.7)
PKD1 IF indel	32	58.6 (54.9 to 62.4)	71.6 (67.3 to 75.9)
PKD1 NT	152	70.8 (67.5 to 74.2)	77.5 (74.6 to 80.5)
PKD2	213	80.0 (77.1 to 82.8)	79.1 (76.6 to 81.6)
NMD	61	77.5 (72.1 to 82.9)	80.1 (75.3 to 84.8)

[a]Data derived from Kaplan–Meier survival analysis and expressed as means and 95% CIs. $P<0.001$ by log-rank test.

J Am Soc Nephrol 2016, in press

ADPCKD:
Mutation Databse (PKDB)

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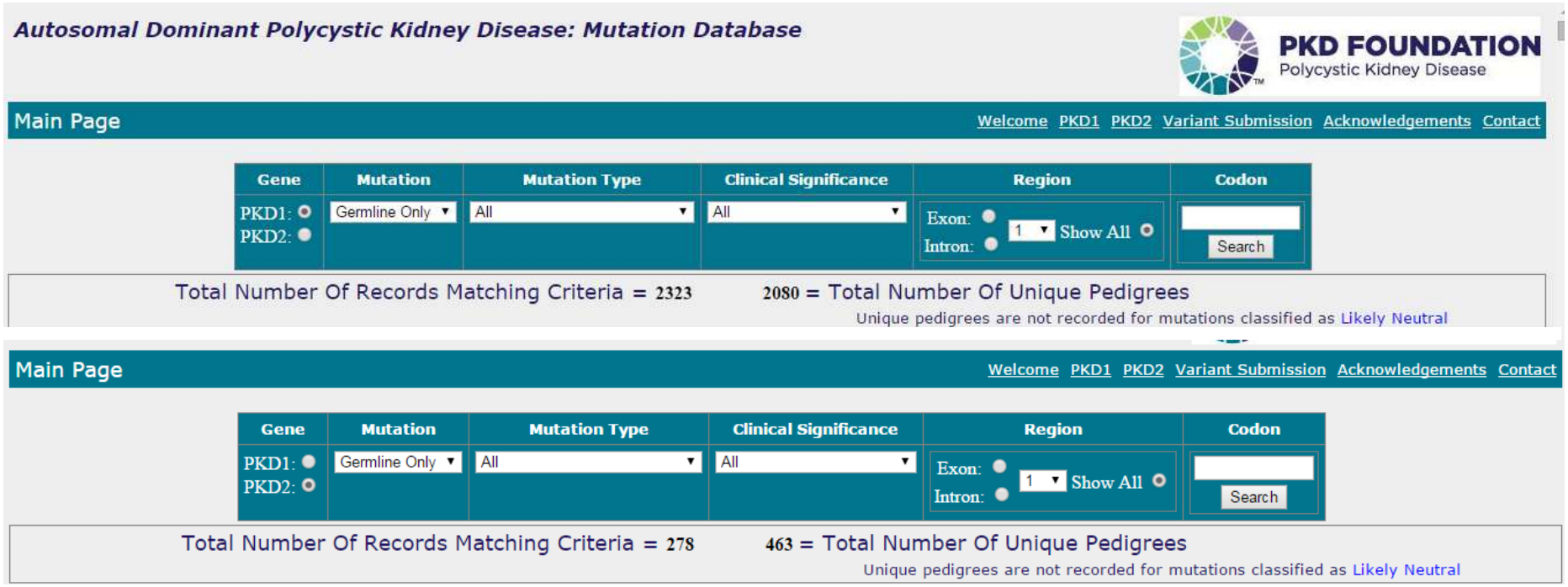
http://pkdb.mayo.edu/



ADPCKD: PROPKD Score

CLINICAL RESEARCH www.jasn.org

The PROPKD Score: A New Algorithm to Predict Renal Survival in Autosomal Dominant Polycystic Kidney Disease

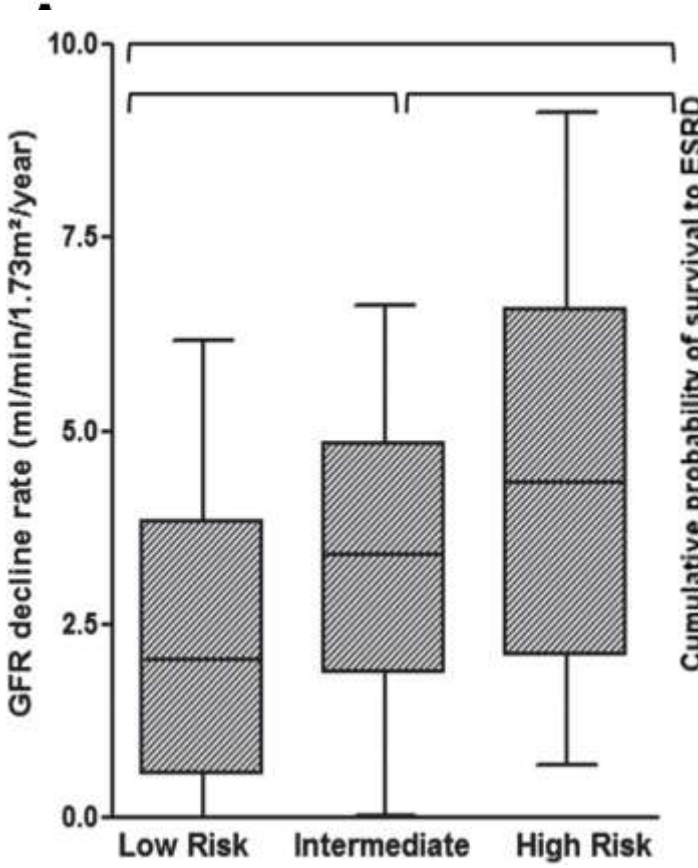
Multivariate Cox analysis

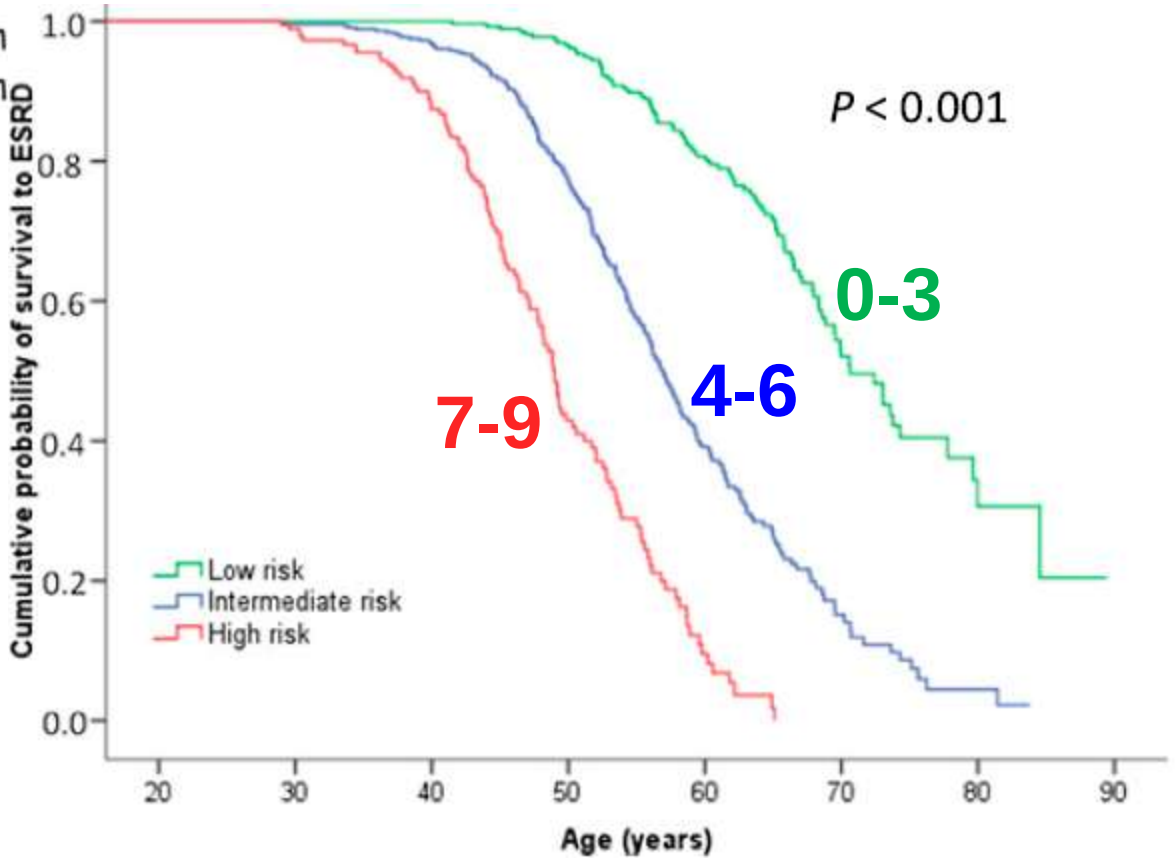
Variable	Patients (*n*)	HR (95% CI)	95% CI from Bootstrap Analysis	*P* Value	Points for PROPKD Score
Sex					
Female	541				0
Male	432	1.55 (1.29 to 1.88)	1.27 to 1.89	<0.001	1
Hypertension before age 35 yr					
No	679				0
Yes	294	2.11 (1.71 to 2.61)	1.71 to 2.62	<0.001	2
≥1 urologic event before age 35 yr					
No	734				0
Yes	239	1.73 (1.38 to 2.18)	1.35 to 2.24	<0.001	2
Mutation					
PKD2	186				0
PKD1 nontruncating	239	2.27 (1.57 to 3.28)	1.61 to 3.18	0.002	2
PKD1 truncating	548	4.75 (3.41 to 6.60)	3.63 to 6.60	<0.001	4

95% CI, 95% confidence interval.

J Am Soc Nephrol 2016, in press

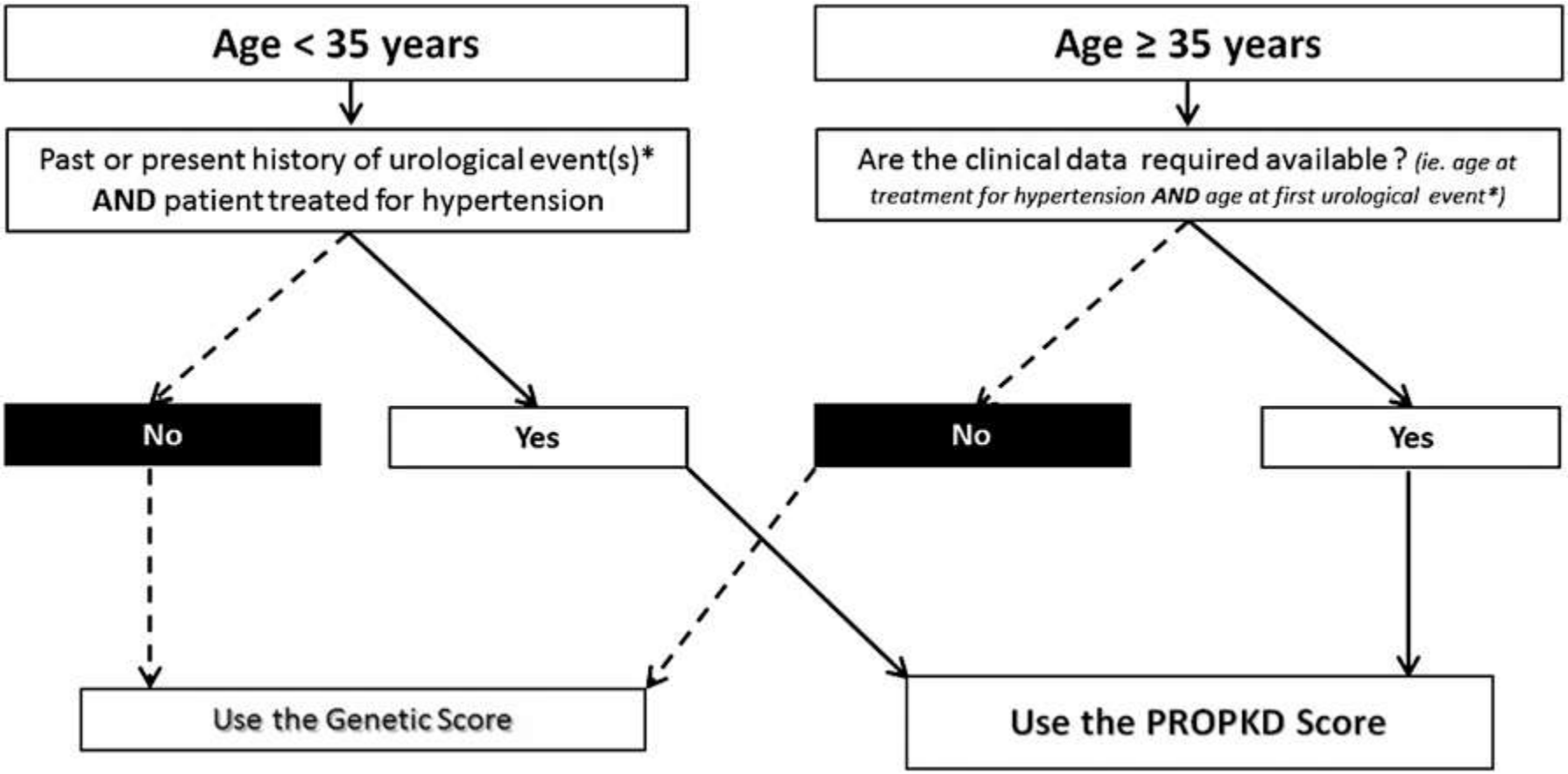
ADPCKD:
PROPKD Score





J Am Soc Nephrol 2016, in press

ADPCKD:
PROPKD Score



J Am Soc Nephrol 2016, in press

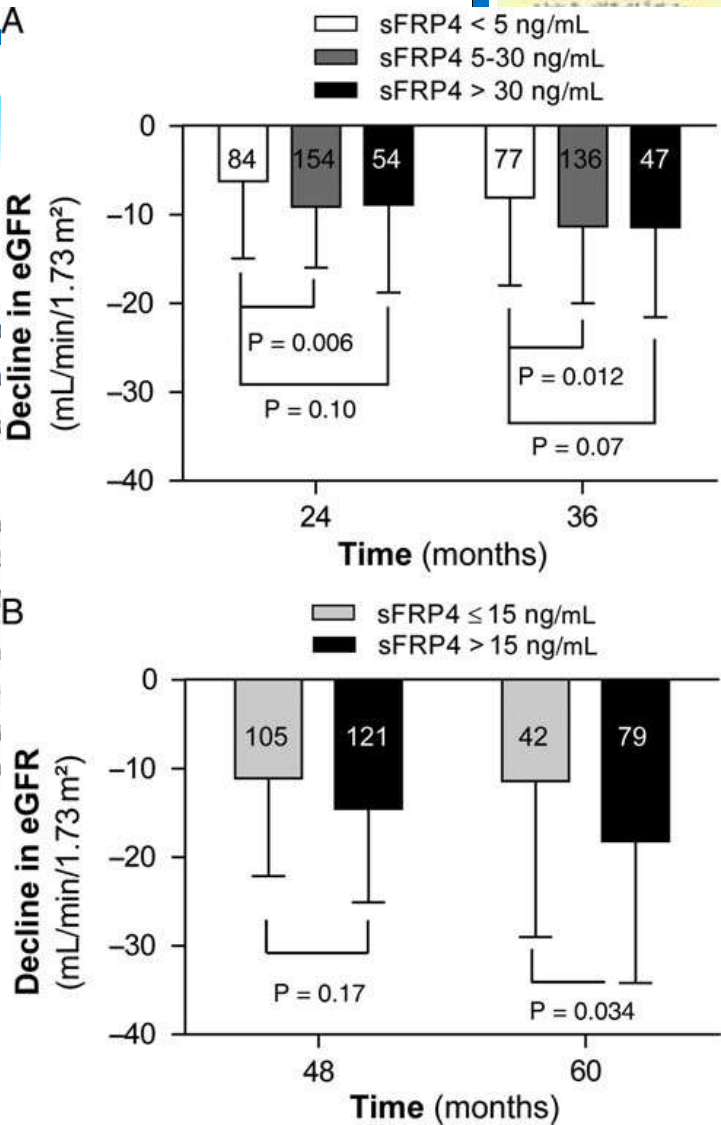
ADPCKD: sFRP4

Urology and Nephrology Center

Secreted frizzled-related protein 4 predicts progression of autosomal dominant polycystic kidney disease

Stefan Zschiedrich[1], Klemens Budde[2], Jens Nürnberger[3], Christoph Wanner[4], Claudia Sommerer[4], Ulrich Kunzendorf[6], Bernhard Banas[7], Walter H. Hoerl[8,†], Nicholas Obermüller[9], Wolfgang Arn[10], Hermann Pavenstädt[11], Jens Gaedeke[2], Tom H. Lindner[12], Lothar Faerber[13], Peter Wimmer[13], Rol[14], Kai-Uwe Eckardt[15] and Gerd Walz[1]

[1]Renal Division, University Hospital Freiburg, Freiburg, Germany, [2]Renal Division, Charité Universitätsmedizin Berlin – Campu[s] Germany, [3]Department of Nephrology, Helios Kliniken Schwerin, Schwerin, Germany, [4]Renal Division, University Hospital Wü[rz] Würzburg, Germany, [5]Center for Nephrology, University Hospital Heidelberg, Heidelberg, Germany, [6]Renal Division, Universit[y] Kiel, Germany, [7]Renal Division, University Hospital Regensburg, Regensburg, Germany, [8]Department of Internal Medicine III, [9] Hospital, Vienna, Germany, [9]Renal Division, Center for Internal Medicine, University Hospital Frankfurt, Frankfurt, Germany, [10] Nephrology, Merheim Medical Center, Cologne, Germany, [11]Renal Division, University Hospital Münster, Münster, Germany, [12] University Hospital Leipzig, Leipzig, Germany, [13]Novartis Pharma GmbH, Nuremberg, Germany, [14]Thermo Fisher Scientific, Frei[burg] and [15]Department of Nephrology and Hypertension, Friedrich-Alexander-University Erlangen-Nürnberg (FAU), Erlangen, Ger[many]



Nephrol Dial Transplant (2016) 31: 284–289

ADPCKD:
MRI Automated Segmentation

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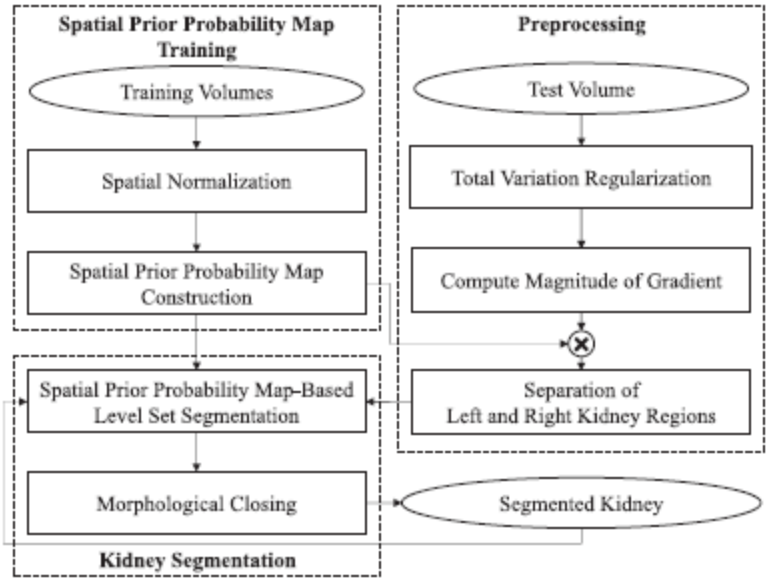
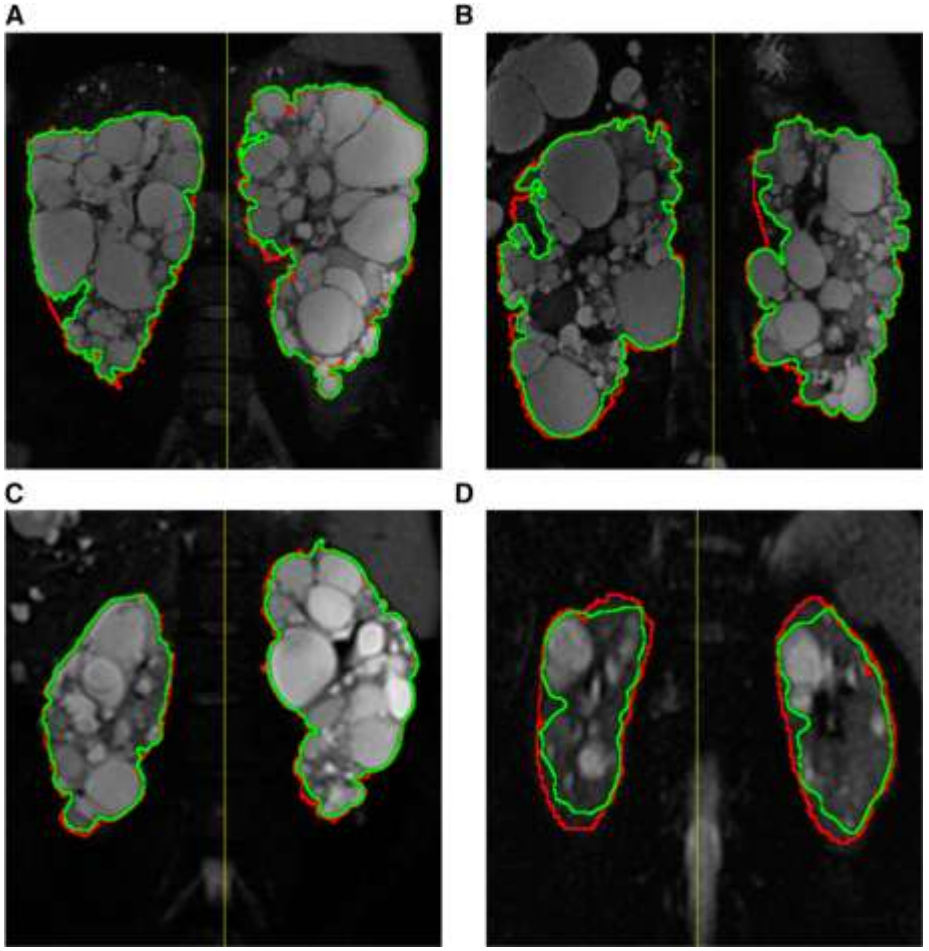
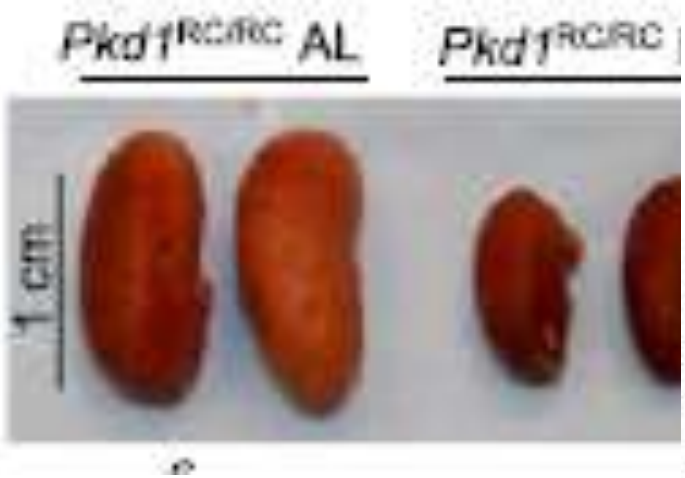
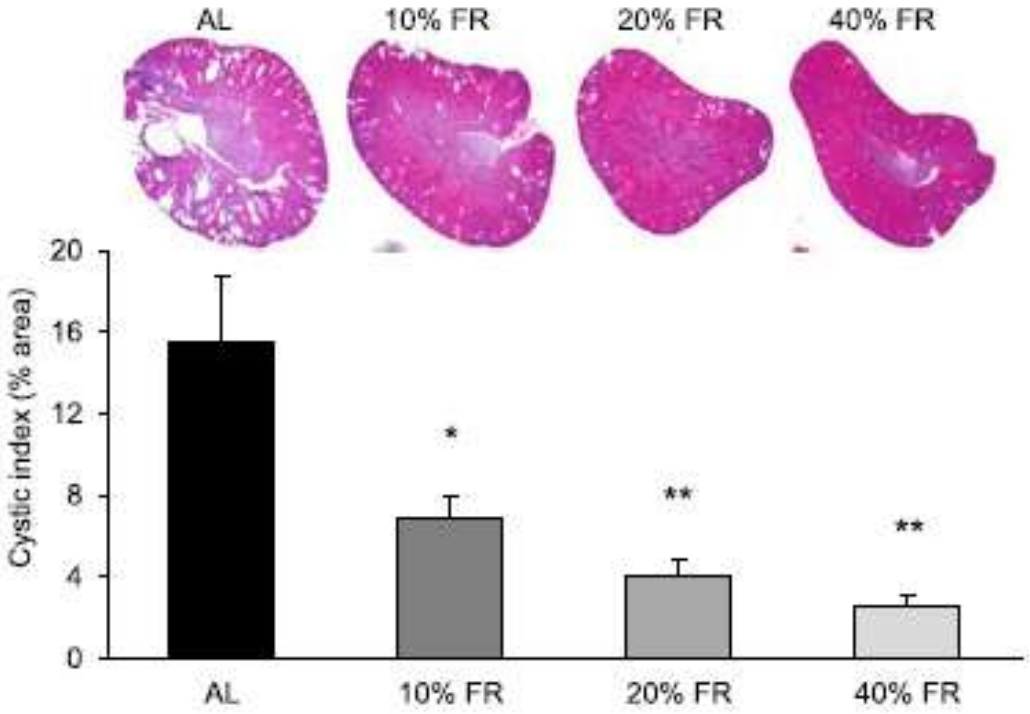




Clin J Am Soc Nephrol 11: ccc–ccc, April, 2016

Food Restriction and ADPCK





J Am Soc Nephrol 2016, in press

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5

African American

APOL1-Associated Diseases

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DNG

Clinical and Population Studies

APOL1 Genotype, Kidney and Cardiovascular Disease, and Death in Older Adults

Kenneth J. Mukamal, Joseph Tremaglio, David J. Friedman, Joachim H. Ix, Lewis H. Kuller, Russell P. Tracy, Martin R. Pollak

Arterioscler Thromb Vasc Biol. Feb 2016;36:398-403

CKD-MBD:
African Ancestry

CJASN ePress. Published on February 8, 2016 as doi: 10.2215/CJN.08020715

Article

Genetic African Ancestry and Markers of Mineral Metabolism in CKD

Orlando M. Gutiérrez, Afshin Parsa, Tamara Isakova, Julia J. Scialla, Jing Chen, John M. Flack, Lisa C. Nessel, Jayanta Gupta, Keith A. Bellovich, Susan Steigerwalt, James H. Sondheimer, Jackson T. Wright Jr, Harold I. Feldman, John W. Kusek, James P. Lash, and Myles Wolf

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6

Clinical Implications and Guidelines

Genetic Testing: Clinical Implications

- **Provides a definitive diagnosis**
- **Enables genetic counselling for family planning**
- **Enables unnecessary diagnostic procedures, tests and treatments to be avoided**
- **Early detection and treatment of asymptomatic (or subtle) extrarenal manifestations**

Nature Reviews | Nephrology Published Online 11 Jan 2016

European Renal Best Practice Guideline

1.4.4. We do not recommend living donation from a genetically related donor in patients who are suspected to have atypical HUS as their underlying kidney disease unless the responsible mutation has been conclusively excluded in the donor. (**1D**)

1.5.5. We suggest that children with steroid-resistant nephrotic syndrome undergo appropriate genotyping before wait-listing them for kidney transplantation. (**Ungraded Statement**)

Parma, Italy, [11]Renal Unit, Azienda Ospedaliero-Universitaria Careggi, Florence, Italy, [12]Medical Faculty, University Department of Nephrology, Skopje, Republic of Macedonia, [13]Department of Abdominal Surgery and Transplantation, CHU Liege, Liège, Belgium, [14]Transplantation Immunology and Nephrology, University Hospital Basel, Basel, Switzerland, [15]Center for Biomedical Research of the Canary Islands (CIBICAN), University of La Laguna, La Laguna, Spain, [16]Nephrology Service, University Hospital of Canary Islands, La Laguna, Spain, [17]Nefrología, Instituto Reina Sofía de Investigación, Madrid, Spain, [18]Department of Nephrology, Institute for Clinical and Experimental Medicine, Prague, Czech Republic, [19] Department of Nephrology, University of Heidelberg, Heidelberg, Germany, [20]Department of Nephrology, University Hospital Ghent, Ghent, Belgium, [21]Dienst Nefrologie, UZ Gent, Gent, Belgium and [22]Renal Division, University Hospital Ghent, Ghent, Belgium

Nephrol Dial Transplant (2015) 30: 1790–1797

ADPCKD:
Genetic Counseling

KIDNEY HEALTH AUSTRALIA | CARI GUIDELINES

KHA-CARI Autosomal Dominant Polycystic Kidney Disease Guideline: Counseling

GUIDELINE RECOMMENDATIONS*

a. We recommend that adult patients diagnosed autosomal dominant polycystic kidney disease referred to their regional genetics service for g counseling if they are interested in and would discuss (2B) the following:
   i. Inheritance pattern and clarifying/commu ing disease risk to family members
   ii. Molecular genetic testing (role, indication interpretation)
   iii. Family planning and prenatal testing options (including preimplantation genetic diagnosis)

b. We recommend adults and children at risk of autosomal dominant polycystic kidney disease are referred to their regional genetics service for genetic counseling if they are interested in and would like to discuss (2A) the following:
   i. Inheritance pattern and their risk of disease
   ii. Predictive testing (via renal imaging and/or molecular genetic testing) and associated issues
   iii. Family planning and prenatal testing options (including preimplantation genetic diagnosis)

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Closure

Novel Genetic Causes:
A new Dimension of GRD

STUDY PROTOCOL Open Access

A protocol for the identification and validation of novel genetic causes of kidney disease

Andrew Mallett[1,2,3,16*], Chirag Patel[4], Barbara Maier[3,5], Julie McGaughran[4], Michael Gabbett[4,6], Minoru Takasato[3,5], Anne Cameron[2], Peter Trnka[7], Stephen I. Alexander[8], Gopala Rangan[9], Michel C. Tchan[10], Georgina Caruana[11], George John[1], Cathy Quinlan[12], Hugh J. McCarthy[8,10], Valentine Hyland[13], Wendy E. Hoy[2], Ernst Wolvetang[14], Ryan Taft[3], Cas Simons[3], Helen Healy[1,2] and Melissa Little[3,5,15]

[1]Kidney Health Service and Conjoint Kidney Research Laboratory, Royal Brisbane and Women's Hospital, Brisbane, Australia
[2]Centre for Kidney Disease Research, Centre for Chronic Disease and CKD.QLD, School of Medicine, The University of Queensland, St Lucia, Australia

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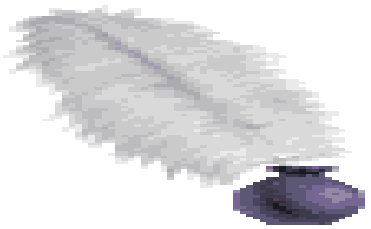
Nephrogenetics:
Limitations and Challenges

- Study design
- Phenotypic/genotypic heterogeneity
- Regulatory and ethical concerns
- Lack of cost effectiveness analyses
- Limited availability and lack of education



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DNG Delcanbo Nephrology Group

YouTube EG

Genetics and update of CKD

Hussein Sheashaa, MD, FACP

Professor of Nephrology, Urology and Nephrology Center and Director of Medical E-Learning Unit, Mansoura University and Executive Director of ESNT-Virtual Academy: http://lms.mans.edu.eg/esnt

ESNT, February 23rd , 2016

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